

## V. NICOTINE USE IN PERSPECTIVE

### 1. Introduction

When evaluating nicotine use and the smoking habit it is important to compare nicotine with other substances which are habitually used and compounds which produce similar effects. Comparisons with reference substances are an essential part of the assessment of any therapeutic agent so that the relative costs and benefits can be estimated and decisions made about the agent's usefulness. In the case of nicotine, which has stimulant and sedative properties, the selected reference agents are the psychostimulants, amphetamine and caffeine, and the sedatives, diazepam (Valium) and alcohol. In addition we have also included marijuana (active ingredient is  $\Delta^9$ -tetrahydrocannabinol or THC), which is inhaled for its pleasurable effects.

The comparison takes the form of an analysis of both the pharmacokinetic and pharmacodynamic features of these substances which could constitute risk to the user. The important pharmacokinetic features are absorption, user control of dose, duration of action, side effects that would impair normal functioning (acute toxicity), chronic toxicity in terms of damage to brain and body, and abuse potential.

### 2. Absorption

As we have seen, nicotine inhaled into the lungs, is readily absorbed and travels from the pulmonary vein to the brain within ten seconds to reach peak concentration immediately after the last puff of the cigarette, ie about seven minutes after lighting up (see Section II). An oral dose of alcohol must travel through the stomach, where some absorption may occur depending on the stomach contents, to the major site of rapid absorption in the small intestine. Gastric emptying time and thus the onset of absorption results in a variable rate of uptake so that peak concentrations of alcohol in plasma are reached between 40 minutes and 120 minutes (Lemberger and Rubin, 1976). Diazepam is also absorbed from the

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gastrointestinal tract and several hours are needed to achieve peak blood and brain levels (Kornetsky, 1976). Amphetamine and caffeine are absorbed from the stomach and peak concentrations in plasma and brain are reached about 30 minutes after an oral dose of caffeine (Marks and Kelly, 1973) and between one and three hours after an oral dose of amphetamine (Beckett, 1970). Amphetamine is also taken intravenously and peak doses in the brain can be achieved within five minutes (Lemberger and Rubin, 1976). The absorption of THC into the bloodstream is rapid when inhaled and it passes rapidly to the brain, but uptake into the brain is slow so that only one per cent appears in rat brain at 60 minutes (Lemberger and Rubin, 1976). Obviously, nicotine reaches potential active sites in the brain very quickly in comparison with these reference substances.

Absorption time is significant for personal control of effect and prevention of over-dosing; a fast absorption time enables the user to adjust his dose to his requirements and so control the magnitude of effect. An ideal agent for self-medication would enable the person to fit the dose to his needs. Smokers have puff by puff control with brain effects occurring within 10 seconds while a drinker must choose an "appropriate" dose for effects in an hour or so. Thus in terms of personal control the experienced smoker has precise control over nicotine's psychoactive effects whereas most drinkers have very haphazard control. Precision of control is also particularly important when considering toxicity because the risk of exceeding the optimal dose is minimised.

### 3. Duration of Action

A second aspect of pharmacokinetics, which is also related to personal control of a person's psychological state, is duration of action. Psychological needs vary and most people want coping techniques for specific occasions rather than for chronic states. Thus stimulation may be needed for an arduous task but not some hours later at bedtime; anxiety reduction is required for a 10 minutes interview with a director but not for interacting with colleagues.

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Nicotine has a half-life of only 20 minutes and is cleared from the body in about 40 minutes (see Section II). In comparison, alcohol (Beckett, 1970) and caffeine (Marks and Kelly, 1973) have half-lives in the range of 3-4 hours and both may remain in the body for 8-12 hours (Gilbert, 1976). Although these values are several orders of magnitude more than for nicotine they are insignificant in comparison with the 20-50 hours for the elimination half-life of diazepam (Breimer, 1979) and 56 hours for THC (Lemberger and Rubin, 1976). In addition, diazepam and THC have active metabolites that further prolong their action while cotinine the major metabolite of nicotine seems to be virtually inactive.

Clearly nicotine fits the pharmacokinetic specifications of a compound which a person can use to self medicate and exert fine control over his psychological state on an hour by hour basis.

#### 4. Specificity of Action

One of the important pharmacodynamic criteria for a therapeutically useful agent is that it is relatively specific in its mode of action. Ideally it should be a "magic bullet" that moves specifically to the target site and exerts its action at no other loci. Much more common among psychoactive substances are those which act on several biochemical systems even at low doses. The acetylcholine, dopamine, noradrenalin and serotonin systems are all modified directly by alcohol (Israel and Mardones, 1971), caffeine (Gilbert, 1976) diazepam (Warburton, 1975) and THC (Harris, 1978). In contrast, amphetamine which only acts on the dopamine and noradrenalin systems, is relatively specific (Lemberger and Rubin, 1976). From the balance of evidence available, smoking doses of nicotine only act directly on some of the acetylcholine systems in the body (the so called "nicotinic" pathways). Nicotine's molecular structure is similar enough to the acetylcholine molecule to mimic it and so produce normal changes in these pathways. This specificity of action decreases the likelihood that a drug will produce unwanted "side effects". This aspect will be discussed in more detail in the next section on toxicity.

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## 5. Toxicity

Almost all substances have toxic effects if taken in large doses for a sufficiently long period of time. In this section we will consider the acute, unwanted effects of the reference compounds and the chronic consequences of normally-used doses taken over a long period of time.

Although amphetamine can improve performance in laboratory tests there is evidence that the drug also distorts judgement so that the subject believes that the improvement is greater than it is. As well as distorting judgement, amphetamine acts as a sleep and appetite suppressant, and chronic use of the drug invariably leads to loss of weight due to reduced food intake. Repeated use of the drug results in tolerance so that higher and higher doses are needed to obtain the stimulant effects. Frequent small doses of amphetamines produce psychotic episodes in normal subjects (Kornetsky, 1976) and repeated use of high doses result in severe psychosis. Obviously amphetamine use is fraught with risks.

Caffeine is a much less harmful stimulant than amphetamine but is not without toxic effects. Gilbert (1976) reviewed the literature and concluded that there is considerable risk to the health of an average adult from the consumption of over 600 mg of caffeine a day (about eight cups of coffee). Such an adult will be more likely to experience headaches, insomnia, anxiety and depression on waking. Repeated use increases the likelihood of myocardial infarction, stomach ulcers, duodenal ulcers, and carcinoma of the kidneys and urinary tract. Recently it has been implicated with pancreatic cancer (MacMahon et al, 1981). Clearly, caffeine is not an entirely harmless compound although it is a much safer, but less potent, psychostimulant than amphetamine.

In view of alcohol's non-specific biochemical action it is not surprising that moderate doses of alcohol have a variety of acute unwanted consequences. It has a general, non-selective effect on all neural systems which lead to impairment of all types of performance eg thought, memory, concentration, fine movement, and motor control. As a consequence, anxiolytic doses are incompatible with most types of work. Moderate drinking probably cause very little chronic toxicity in terms of psychological and physiological functioning but repeated use of the drug

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results in larger and larger doses being required for anti-anxiety effects. Long term use of larger amounts leads to deterioration of the brain, liver and other organs (Wallgren and Barry, 1971).

The most common side effects of diazepam is drowsiness and impairment of concentration. These acute toxic effects are small but not insignificant in a fit, unfatigued person who has taken no alcohol, but are hazardous in a tired person or someone who has taken even a small amount of alcohol. It should also be remembered that the drug persists in the body for days and so the alcohol interaction could occur long after taking a dose. The evidence for chronic toxicity with diazepam is small and, although some tolerance develops, there is not the dramatic escalation of doses that can occur with alcohol (Marks, 1978). From the point of view of acute and chronic toxicity diazepam is a much safer anxiolytic than alcohol.

Alcohol use is often compared unfavourably with marijuana use, but the problem with this toxicity comparison is that we know so little about  $\Delta^9$ -tetrahydrocannabinol (THC) and its active metabolites. Performance testing has revealed that cognitive ability and reaction time are impaired and, not surprisingly, driving skills (see review in Warburton, 1975 and Kornetsky, 1976). There is no evidence that repeated casual use has adverse consequences but an amotivational syndrome after frequent use of marijuana has been reported (Warburton, 1975; Kornetsky, 1976).

A typical list of the toxic effects of nicotine includes sweating, tremor, nausea, vomiting, abdominal pain, diarrhoea, palpitation, fatigue and headache (Cohen and Roe, 1981) but of these symptoms only tremor occurs in experienced smokers which suggests that either tolerance to these effects has occurred or the smoker titrates his dose to avoid the unwanted adverse effects. There is no evidence of intellectual impairment during use and, on the contrary, nicotine improves psychological performance (see Section IV D). This benign action seems to be due to the similarity between nicotine and acetylcholine, so that nicotine acts in a natural way on neurones and only produces changes in the brain which occur normally in states of alertness. As a consequence of its similarity to acetylcholine, tolerance to its action on electrocortical arousal does not occur (Murphree, 1979). This lack of tolerance is not surprising because neurones cannot become tolerant to their own chemicals otherwise they would cease to

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function. Without tolerance to the desired effects, smokers do not have to keep on increasing the dose to achieve the desired amounts of sedation or stimulation. Evidence for chronic toxicity due to nicotine alone, rather than cigarette smoke, is sparse and there is little convincing evidence of intellectual impairment even after a lifetime of use. Chronic nicotine use has sometimes been linked to gastrointestinal disturbance and cardiovascular disorders but no studies have controlled for caffeine and alcohol consumption which are associated with both sorts of disorder. Thus, nicotine, in smoking doses, has little known toxicity itself and the hazard to the smoker is in the other smoke constituents.

In summary, the ranking of compounds for toxicity, considering the doses which are in general use, would be alcohol (severe toxicity with potentially severe chronic toxicity), amphetamine (minor acute toxicity but severe chronic toxicity), marijuana (acute toxicity and perhaps minor chronic toxicity) caffeine (minor acute toxicity and moderate chronic toxicity), diazepam (minor acute toxicity and little chronic toxicity), and nicotine (no acute toxicity in smoking doses and little known chronic toxicity).

#### 6. Abuse Potential

Use of any substance can only be evaluated with respect to the situation of use, the manner of use as well as the consequences of use (Balter, 1974). Normal use can be defined as consumption for an innocuous or constructive purpose in moderate amounts and in the appropriate context in terms of place and culture. Abuse focuses on adverse consequences of use in terms of physiological or psychological effects. The consequences of abuse are organ damage and impairment of social and personal functioning. Indirectly, abuse refers to the manner of use by the person (pattern and amount taken). The problem of abuse is in the person's interaction with the compound and is not a fault of the compound itself. However, some substances are more likely to lead to abuse than others and this aspect is referred to as abuse potential. The abuse potential of a substance can be defined in terms of its intrinsic attractiveness (Balter, 1974), the number of users (Balter, 1974) and the number of users who become abusers of the substances (Balter, 1974).

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## 7. Intrinsic Attractiveness

Attractiveness refers to the extent to which most users find the immediate effect of a substance intrinsically pleasing. Intrinsic attractiveness is independent of cultural factors and can be assessed from laboratory studies with animals. In the laboratory, animals learn to lever press in order to self-administer some drugs and intrinsic attractiveness is assessed from the ease of learning and the regularity of pressing. While animals will rapidly self-administer amphetamines showing the high intrinsic attractiveness of this compound, animals self-administer alcohol and THC to a much lesser extent showing that these compounds have less intrinsic attractiveness. There is no evidence that animals will self-administer diazepam or caffeine at all, indicating negligible intrinsic attractiveness. Attempts to train animals to self inject nicotine or "to smoke" have been rather unsuccessful which suggests very low intrinsic attractiveness (Kumar, 1979).

These laboratory studies fit with human comparisons of the compounds which indicate that intravenous amphetamine produces pleasure like a "pharmacogenic" orgasm, alcohol and THC produce moderate euphoria, while caffeine produces stimulation but no euphoria and diazepam is pleasurably relaxing but does not produce euphoria. Nicotine can be either mildly stimulating or pleasurably relaxing depending on the situation, but is not a euphoriant. The production of euphoria seems to be essential for high intrinsic attractiveness and for strong habit formation.

The strength of habit formation for non-durable commodities has been estimated by economists by time series analyses of demand (see Houthakker and Taylor, 1966). In their equations they include a parameters for the psychological "stock" of consumption habits because for some commodities, demand does not adjust to changes in prices or income. Current consumption is positively influenced by use of the commodity in the more or less recent past indicating some degree of habit formation. If a smoker has built up a psychological "stock" of smoking habits, then the number of cigarettes that have been smoked in the past will influence current consumption. If we consider the same population (eg United States 1929-1960, before any of the health campaigns), then we can compare the psychological "stock" for

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tobacco consumption with that for alcohol consumption by using the estimates for this parameter in the demand equations. These estimates show that tobacco use was subject to some habit formation (positive parameter value of 0.1743) but it was much smaller than psychological "stock" for alcohol consumption (parameter value of 1.0869). This conclusion would be consistent with the information on relative intrinsic attractiveness of alcohol and nicotine.

In summary, amphetamine produces a very pleasing effect on most people. Alcohol and THC are moderately attractive while caffeine, nicotine and diazepam have little intrinsic attractiveness.

#### 8. Percentage of Abusers

An abuser is a person who is consuming a drug in sufficient quantities to produce damage to health. A comparison of the number of users and abusers is difficult because nicotine, caffeine and alcohol are readily available while amphetamine and diazepam are controlled and marijuana (THC) is illegal. However, the pattern of available evidence is consistent with the data on intrinsic attractiveness. When amphetamines were freely available on prescription in Britain, 10% of the population of Newcastle were receiving amphetamine prescriptions and 20% of the users were abusing the compound (Kiloh and Brandon, 1962). Alcohol and caffeine are socially acceptable substances which are consumed by over 95% of the population in most Western cultures and of these about 5-7% abuse alcohol (Kissin, 1972) and about 3% are caffeine abusers (Gilbert, 1976). It is estimated that 5-7% of THC users are abusers (Kissin, 1973). Abusers of diazepam are rare and current estimates would place the percentage at less than 1% (Marks, 1976). Strictly speaking, the number of abusers of nicotine is zero since few individuals take pure nicotine and nicotine itself is not known to contribute to the smoke-related disorders (Cohen and Roe, 1981).

Abuse potential has also been defined in terms of difficulty of stopping use. Of the reference substances, comparable data are only available on alcohol and smoking. Hunt and Baspalec (1974) compared the relapse rates for alcoholics and smokers with heroin (an agent with very high intrinsic attractiveness) and found that the relapse curves were very

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similar. This similarity has been used as evidence for the strong abuse potential of nicotine and for a common mechanism underlying use of all these substances. However, as Jaffe and Jarvik (1978) point out, while one may wonder what drives a heroin abuser to relapse in the face of the social disapproval, the physical hazards and legal risks of heroin use, it is surprising that relapse among ex-smokers is not universal given the multiple motives for smoking and the fact that a heavy smoker will experience the beneficial effects of stimulation or sedation from nicotine hundreds of times a year.

In summary, the overall rankings for abuse potential of the substances in terms of intrinsic attractiveness and number of users is amphetamine, alcohol, marijuana, caffeine with diazepam and nicotine having virtually zero abuse potential.

#### 9. Conclusions

Nicotine, as used by the smoker, is a low risk substance in terms of acute and chronic toxicity and the smoke-related diseases can only be due to the other smoke constituents. Its rapid uptake into the brain allows smokers to control their psychological state at will so that they can obtain either stimulation or sedation to help them to cope with situations. Nicotine's specific action on the brain produces neural changes which are within normal limits and so nicotine acts in a normal way to produce stimulation and sedation. Nicotine is not like other so called "addictive" substances and has low abuse potential. The smoking habit is so strong because of the ability of nicotine to provide smokers with exquisite personal control over their psychological functioning. If future research could reduce those smoke constituents that produce toxicity then people, who need the benefits of nicotine, could obtain these without risk. Certainly no comparable, lower risk compounds are available at the moment.

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